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10/598,682	07/30/2007	Alberto Hayek	24978-0047	8815

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EXAMINER	
ROMEO, DAVID S	

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1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/598,682	HAYEK ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-12,14-23,25-29,31-44,46,61,62 and 65* is/are pending in the application.

4a) Of the above claim(s) *3,5,18-23,25-29,31-44,46,62 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-12,14-17 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0307,1107*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 11/29/2010 has been entered. Claims 1, 3, 5-12, 14-23, 25-29, 31-44, 46, 61, 62 and 65 are pending.

Election/Restrictions

In view of the amendment filed 11/29/2010 the restriction required is modified as indicated below. Applicant's elected group I, drawn to a method comprising exposing a stem cell to Activin A, in the response filed 11/29/2010. In view of the fact that all of the amended claims to the elected invention, i.e., a method comprising exposing a stem cell to Activin A, are within the revised group I below, applicants' election constructively elects the revised group I below for prosecution on the merits.

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1, 6–12, 14-17 and 61, drawn to a method comprising exposing a stem cell to Activin A.

Group II, claim(s) 3, 5 and 18-22 (in part), drawn to a method comprising exposing a stem cell to Activin A and an FGF family member.

Group III, claim(s) 3 and 5 (in part), drawn to a method comprising exposing a stem cell to Activin A and NIC.

Group IV, claim(s) 3 and 5 (in part), drawn to a method comprising exposing a stem cell to Activin A, an FGF family member and NIC.

Group V, claim(s) 23, 25–29, 31-39 and 62 (in part), drawn to a composition comprising Activin A and an FGF family member.

Group VI, claim(s) 23, 25–29, 31-39 and 62 (in part), drawn to a composition comprising Activin A and NIC.

Group VII, claim(s) 23, 25–29, 31-39, 40-44, 46 and 62 (in part), drawn to a composition comprising Activin A, an FGF family member and NIC.

Group VIII, claim(s) 65, drawn to a composition comprising a stem cell.

The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. Whether or not any particular technical feature makes a "contribution" over the prior art, and therefore constitutes a "special technical feature," is considered with respect to novelty and inventive step. The special technical feature of groups I–VII is Activin A. The prior art rejections in the instant Office action show that there is a lack of novelty or inventive step with respect to this special technical feature. Therefore, the inventions of groups I-VII do not fulfill the requirements for unity of invention. The special technical feature of group VIII is a stem cell produced by a process. The process limitation is not viewed as positively limiting the claimed stem cell, as it is assumed that equivalent products are obtainable by multiple routes. Ying (Cell 115, 281-292 (2003)), as indicated previously, and the prior art documents in the prior art rejections in the instant Office action disclose stem cells. Therefore, group VIII does not fulfill the requirements for unity of invention and does not involve the same or corresponding special technical feature with groups I-VII.

Applicant's election with traverse of group I, drawn to a method comprising exposing a stem cell to Activin A, in the reply filed on 11/29/2010 is acknowledged. The traversal is on the ground(s) that the groups relate to single inventive concept because they share the same corresponding technical feature, which is the combined use of Activin A optionally with FGF family members and NIC. This is not found persuasive

because the prior art rejections in the instant Office action show that there is a lack of novelty or inventive step with respect to culturing stem cells with activin A. Therefore, this special technical feature does not fulfill the requirements of unity of invention. Insofar as the special technical feature of culturing stem cells with activin A does not fulfill the requirements of unity of invention, then group I does not share the same or corresponding special technical feature with culturing a stem cell with Activin A and an FGF family member (group II), culturing a stem cell with Activin A and NIC (group III), culturing a stem cell with Activin A, an FGF family member and NIC (group IV), a composition comprising Activin A and an FGF family member (group V), a composition comprising Activin A and NIC (group VI), or a composition comprising Activin A, an FGF family member and NIC (group VII). Insofar as activin A is not a special technical feature, then each of the special technical features of groups II-VII, as indicated above, is different.

The special technical feature of group VIII is a stem cell produced by a process. The process limitation is not viewed as positively limiting the claimed stem cell, as it is assumed that equivalent products are obtainable by multiple routes. Ying (Cell 115, 281-292 (2003)), as indicated previously, and the prior art documents in the prior art rejections in the instant Office action disclose stem cells. Therefore, group VIII does not fulfill the requirements for unity of invention and does not involve the same or corresponding special technical feature with groups I-VII.

Therefore, the inventions of groups I-VIII do not fulfill the requirements for unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 3, 5, 18-23, 25-29, 31-44, 46, 62 and 65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/29/2010.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

The application is not fully in compliance with the sequence rules, 37 C.F.R. § 1.821-1.825. Specifically, the specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. See pages 51-52. This is not meant to be an exhaustive list of places where the specification fails to comply with the sequence rules. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. The application cannot issue until it is in compliance. Nucleic acid sequences with 10 or more nucleotides, at least 4 of which are specifically defined, must comply with the sequence rules. Amino acid sequences with 4 or more residues,

at least 4 of which are specifically defined, must comply with the sequence rules. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO: 23" is permissible and the fragment need not be separately presented in the "Sequence Listing."

Correction is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (e.g., http://biomeda.com). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6–12, 14–17 and 61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising culturing HSF6 cells in a cell culture comprising activin-A in an amount sufficient to maintain the cells in an undifferentiated state, does not reasonably provide enablement for a method comprising culturing a stem cell in a cell culture comprising activin-A in an amount sufficient to maintain the cells in an undifferentiated state. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to or encompass a method of maintaining any mammalian, human or embryonic stem cell in an undifferentiated state by exposing the stem cell to activin-A. All of the working examples used a single human stem cell line, HSF6. In other words, the specification only contains a single example of a human stem cell line that responds to activin-A in the manner required by the claimed method. There are no working examples comprising culturing any other stem cell in a cell culture comprising Activin A in an amount sufficient to maintain the stem cell in an undifferentiated state for a sufficient amount of time. The examiner is aware working examples are not required. Lack of a working example is, however, a factor to be considered.

According to the specification:

> [0005] ... it is becoming apparent that the requirements for growth of hESC will be significantly different from those required for growth of mESC.
>
> [0140] Maintenance of the undifferentiated state and pluripotency in mouse ES requires the presence of mouse fibroblast feeder layers (mEFs) or activation of STAT3 with leukemia inhibitory factor (LIF). ...STAT3 activation is not sufficient to block differentiation of human ES cell lines when grown on mEFs or when treated with conditioned media from mEFs.
>
> [0145] The inhibition of differentiation in hES was specific for Activin A. While BMP-4, another TGFβ family member can maintain pluripotency in mouse ES cells,...this is not the case with hES. This is not the only difference between these two cells--mES and hES also differ in their dependence on LIF for maintenance.... In mES cells, BMP-4 plays a paradoxical role in both maintenance of pluripotency and differentiation,... most likely depending on other factors present or on stage of development. hES cells differentiated rapidly in the presence of BMP-4

> and KGF, and expression of oct-4, nanog, and telomerase was lost after 1 week culture.

According to van den Eijnden-van Raaij (Mech Dev. 1991 Feb;33(2):157-65) the action of activin-A in the murine system is completely different from that in the Xenopus system.

Therefore, there is a lack of predictability in the art with respect to the growth of and maintenance of stem cells from different organisms.

Levenberg (Proc Natl Acad Sci U S A. 2003 Oct 28;100(22):12741-6. Epub 2003 Oct 15) discloses a method comprising culturing hES cells (H9 clone) (page 12741, right column, full paragraph 1) in a cell culture comprising activin-A (20ng/ml) (page 12741, right column, last full paragraph; Fig 2A-B). Activin-A induced differentiation of the hES cells into liver-like cells (paragraph bridging pages 12743-12744). Therefore, maintaining one human stem cell line, i.e., HSF6, in an undifferentiated state with activin-A is not predictive of the results with any mammalian, human or embryonic stem cell.

Claim 6 requires growth. Claims 11 and 12 require at least ten or at least thirty passages, respectively. However, according to the specification:

> [0142]...when hES cells were grown on laminin in the presence of Activin A and KGF they remained undifferentiated following continuous growth over 10 passages, ...
>
> [0143] ...when KGF was removed, the cells maintained their undifferentiated phenotype but the proliferation rate decreased and they could not be subcultured beyond one passage.

Clearly, the HSF6 cells did not grow and could not be passaged at least ten or thirty times in the presence of activin-A only. Therefore, there are no working examples of the claimed results in claims 6, 11 and 12 using only activin-A.

In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 7 recite the limitation "said exposing". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8–10 and 61 rejected under 35 U.S.C. 102(a) as being anticipated by Levenberg (Proc Natl Acad Sci U S A. 2003 Oct 28;100(22):12741-6. Epub 2003 Oct 15).

Levenberg discloses a method comprising culturing human embryonic stem cells (hES cells, H9 clone) (page 12741, right column, full paragraph 1) in a cell culture comprising activin-A (20ng/ml) (page 12741, right column, last full paragraph; Fig 2A-B).

The examiner is aware that activin-A induced differentiation of the hES cells into liver-like cells (paragraph bridging pages 12743-12744). However, the claims only require "an amount [of activin-A] sufficient to maintain the stem cell in an undifferentiated state for a sufficient amount of time." The metes and bounds of "for a sufficient amount of time" are not clearly set forth, as discussed above. Therefore, the amount of activin-A was sufficient to maintain the stem cell in an undifferentiated state for a sufficient amount of time in the absence of evidence to the contrary. Also, the amount of activin-A used by Levenberg is within the range of amounts of activin-A contemplated for use in the present invention, as indicated in paragraph 0091 of the present specification.

There is nothing in Levenberg teaching or suggesting that the cell culture comprises a feeder cell, conditioned media or LIF.

Claims 1, 8, 10 and 14–17 are rejected under 35 U.S.C. 102(b) as being anticipated by van den Eijnden-van Raaij (Mech Dev. 1991 Feb;33(2):157-65) in view of

Okazawa (J Cell Biol. 1996 Mar;132(5):955-68), ATCC® Number: CRL-1825™ and GenBank ACCESSION P07995.

A 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to:

(A) Prove the primary reference contains an "enabled disclosure;"
(B) Explain the meaning of a term used in the primary reference; or
(C) Show that a characteristic not disclosed in the reference is inherent.

MPEP § 2131.01.

van den Eijnden-van Raaij discloses a method comprising culturing P19 embryonal carcinoma (EC) cells in a cell culture comprising activin-A (paragraph bridging pages 161-162). Although activin-A has no differentiation-inducing effect on EC cells it probably has a very important regulatory function (paragraph bridging pages 162-163). In the P19 EC aggregation system activin-A is a potent inhibitor or regulator of differentiation during early development (page 163, left column, last full paragraph). The results suggest that activin-A is intimately involved in the regulation of early differentiation processes in vertebrate embryogenesis (Abstract). Activin-A prevents EC differentiation to occur at all. Activin-A possibly acts by disturbing the signals which normally trigger the cells to follow a differentiation program. The action of activin-A in the murine system is completely different from that in the Xenopus system. Other systems more closely related to the in vivo system, will have to be studied in order to elucidate the real function of activin-A in early differentiation events during murine development. See page 164, left column, full paragraph 1.

The prior art recognizes P19 cells as embryonic stem cells. See, for example, Okazawa, Abstract. Accordingly, van den Eijnden-van Raaij's P19 embryonal cell is an embryonic stem cell. Okazawa is cited to explain the meaning of the term "embryonal" used in the primary reference or show that "embryonic" is an inherent property of van den Eijnden-van Raaij's P19 cell.

The P19 line was derived from an embryonal carcinoma induced in a C3H/He mouse. See, for example, ATCC Number CRL-1825. Accordingly, van den Eijnden-van Raaij's P19 cell is a mammalian stem cell. ATCC® Number: CRL-1825™ is cited to show the properties and/or characteristics of van den Eijnden-van Raaij's P19 cell. Therefore, it need not be available as prior art before applicant's filing date. See M.P.E.P. § 2124.

van den Eijnden-van Raaij used recombinant bovine activin-A (page 164, left column, last paragraph). The amino acid sequence of the mature chain of bovine activin-A is identical to the amino acid sequence of SEQ ID NO: 1, as indicated in the following sequence comparison (Qy = SEQ ID NO: 1):

```
Query Match             100.0%;  Score 655;  DB 1;  Length 425;
  Best Local Similarity   100.0%;
  Matches  116;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GLECDGKVNICCKKQFFVSFKDIGWNDWIIAPSGYHANYCEGECPSHIAGTSGSSLSFHS 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        310 GLECDGKVNICCKKQFFVSFKDIGWNDWIIAPSGYHANYCEGECPSHIAGTSGSSLSFHS 369

Qy         61 TVINHYRMRGHSPFANLKSCCVPTKLRPMSMLYYDDGQNIIKKDIQNMIVEECGCS 116
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        370 TVINHYRMRGHSPFANLKSCCVPTKLRPMSMLYYDDGQNIIKKDIQNMIVEECGCS 425.
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The "Db" sequence shown is from GenBank ACCESSION P07995. GenBank ACCESSION P07995 is cited to show the properties and/or characteristics of van den

Eijnden-van Raaij's bovine activin-A. Therefore, it need not be available as prior art before applicant's filing date. See M.P.E.P. § 2124.

The metes and bounds of "for a sufficient amount of time" are not clearly set forth, as discussed above. Therefore, the amount of activin-A was sufficient to maintain the stem cell in an undifferentiated state for a sufficient amount of time in the absence of evidence to the contrary.

There is nothing in van den Eijnden-van Raaij teaching or suggesting that the cell culture comprises a feeder cell or LIF.

Claims 1, 6, 8, 10 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Hashimoto (Biochem Biophys Res Commun. 1990 Nov 30;173(1):193-200) in view of in view of Okazawa (J Cell Biol. 1996 Mar;132(5):955-68), ATCC® Number: CRL-1825™ and Ibelgaufts.

A 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to:

(A) Prove the primary reference contains an "enabled disclosure;"
(B) Explain the meaning of a term used in the primary reference; or
(C) Show that a characteristic not disclosed in the reference is inherent.

MPEP § 2131.01.

Hashimoto teaches that activin acts as a growth factor on undifferentiated P19 cells (Abstract). The cells were cultured in the presence of 1nM activin (page 194, last full paragraph; page 195, last full paragraph). Activin and EDF are identical (paragraph bridging pages 193-194). Ibelgaufts teaches that EDF is an alternate name for activin-

A. Ibelgaufts is cited to explain the meaning of the term "activin" used in the primary reference or show that activin-A is an inherent property of Hashimoto's activin. Ibelgaufts is also cited to show the properties and/or characteristics of Hashimoto's activin. Therefore, it need not be available as prior art before applicant's filing date. See M.P.E.P. § 2124. The metes and bounds of "for a sufficient amount of time" are not clearly set forth, as discussed above. Therefore, Hashimoto's amount of activin was sufficient to maintain the P19 cells in an undifferentiated state for a sufficient amount of time in the absence of evidence to the contrary. The teachings of Okazawa (J Cell Biol. 1996 Mar;132(5):955-68) and ATCC® Number: CRL-1825™ are discussed above and incorporate herein by reference. Briefly, P19 are mammalian stem cells and embryonic stem cells, as evidenced by ATCC® Number: CRL-1825™ and Okazawa (J Cell Biol. 1996 Mar;132(5):955-68), respectively.

Therefore, Hashimoto discloses a method comprising culturing undifferentiated P19 cells in a cell culture comprising activin-A in an amount sufficient to maintain the cells in an undifferentiated state for a sufficient amount of time, wherein the culturing results in growth of the cells.

There is nothing in Hashimoto teaching or suggesting that the cell culture comprises a feeder cell, conditioned media or LIF.

Claims 1, 6-10 and 14-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Xu (Nat Biotechnol. 2001 Oct;19(10):971-4) in view of GenBank ACCESSION NP_032406.

A 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to:

(A) Prove the primary reference contains an "enabled disclosure;"
(B) Explain the meaning of a term used in the primary reference; or
(C) Show that a characteristic not disclosed in the reference is inherent.

MPEP § 2131.01.

Xu discloses a successful feeder-free hES culture system in which undifferentiated cells can be maintained for at least 130 population doublings. In this system, hES cells are cultured in medium conditioned by mouse embryonic fibroblasts. The hES cell populations in feeder-free conditions maintained a stable proliferation rate. The cells retain fundamental characteristics of hES cells in this culture system and are suitable for scaleup production. See the Abstract. Passage numbers are represented as x + y, where x is the passage at which the cells were removed from feeders and y is the number of passages in feeder-free conditions (page 973, right column, § "Human ES culture").

Medium conditioned by mouse embryonic fibroblasts contains abundant amounts of activin A, according to the present specification (paragraph 0144).

Therefore, Xu discloses a method comprising culturing an undifferentiated stem cell in a cell culture comprising activin A in an amount sufficient to maintain the stem in an undifferentiated state for a sufficient amount of time, wherein the culturing results in growth of the cells, wherein the culturing is repeated at least one time, wherein the stem cell is a mammalian, human or embryonic stem cell.

Mouse embryonic fibroblasts would secrete mouse activin A. Mouse activin A comprises the amino acid sequence of SEQ ID NO: 1, as indicated below:

```
  Query Match             100.0%;  Score 655;  DB 1;  Length 424;
  Best Local Similarity   100.0%;
  Matches  116;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GLECDGKVNICCKKQFFVSFKDIGWNDWIIAPSGYHANYCEGECPSHIAGTSGSSLSFHS 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        309 GLECDGKVNICCKKQFFVSFKDIGWNDWIIAPSGYHANYCEGECPSHIAGTSGSSLSFHS 368

Qy         61 TVINHYRMRGHSPFANLKSCCVPTKLRPMSMLYYDDGQNIIKKDIQNMIVEECGCS 116
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        369 TVINHYRMRGHSPFANLKSCCVPTKLRPMSMLYYDDGQNIIKKDIQNMIVEECGCS 424.
```

The "Db" sequence shown is from GenBank ACCESSION NP_032406. GenBank ACCESSION NP_032406 is cited to show the properties and/or characteristics of mouse activin A in Xu's CM. Therefore, it need not be available as prior art before applicant's filing date. See M.P.E.P. § 2124.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over van den Eijnden-van Raaij (Mech Dev. 1991 Feb;33(2):157-65) in view of Okazawa (J Cell Biol. 1996 Mar;132(5):955-68), ATCC® Number: CRL-1825™ and GenBank ACCESSION P07995 as applied to claim 1 above, and further in view of Alak (U. S. Patent No. 5,563,059) and Mason (U. S. Patent No. 4,798,885).

van den Eijnden-van Raaij in view of Okazawa, ATCC® Number: CRL-1825™ and GenBank ACCESSION P07995 teach a method comprising culturing a stem cell in a cell culture comprising conditioned media comprising activin-A, wherein the conditioned media comprises an amount of activin-A sufficient to maintain the stem in an undifferentiated state for a sufficient amount of time, wherein the cell culture does not comprise a feeder cell or LIF, as discussed above. van den Eijnden-van Raaij in view of Okazawa, ATCC® Number: CRL-1825™ and GenBank ACCESSION P07995 do not teach a cell culture, wherein the cell culture does not comprise conditioned media.

One of ordinary skill in the art recognizes that if activin-A is to be used for in vitro culture it can be purified from conditioned media or obtained commercially. See, for example, Alak, column 17, full paragraph 1 and Mason, column 2, lines 35-40. Alak does not teach maintaining stem cells in an undifferentiated state with activin A. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to maintain stem cells in an undifferentiated state with activin-A, as taught by van den Eijnden-van Raaij in view of Okazawa, ATCC® Number: CRL-1825™ and GenBank ACCESSION P07995, and to modify that teaching with a recombinant form of activin A, as taught by Alak, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because large quantities of purified, sterile, pyrogen-free activin A could be obtained economically completely free of extraneous proteins. The invention is prima facie obvious over the prior art.

Claims 1, 7, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hashimoto (Biochem Biophys Res Commun. 1990 Nov 30;173(1):193-200) in view of in view of Okazawa (J Cell Biol. 1996 Mar;132(5):955-68), ATCC® Number: CRL-1825™ and Ibelgaufts as applied to claim 1 above, and further in view of Williams (Nature. 1988 Dec 15;336(6200):684-7).

Hashimoto in view of in view of Okazawa, ATCC® Number: CRL-1825™ and Ibelgaufts teach the maintenance of stem cells in an undifferentiated state with activin-A, as discussed above. Hashimoto in view of in view of Okazawa, ATCC® Number: CRL-1825™ and Ibelgaufts do not teach the maintenance of ES cells in the undifferentiated state for multiple passages or repeating the exposure to activin-A at least one time.

The maintenance of ES cells in the undifferentiated state for multiple passages is of obvious interest to one of ordinary skill in the art. See, for example, Williams, paragraph bridging pages 685-686, paragraph bridging pages 686-687. Williams does not teach the maintenance of stem cells in an undifferentiated state with activin-A.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to maintain stem cells in an undifferentiated state with activin-A, as taught by Hashimoto in view of in view of Okazawa, ATCC® Number: CRL-1825™ and Ibelgaufts, and to modify that teaching by culturing the cells for multiple passages, as taught by Williams, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to assist in the in vitro

analysis of the differentiation of ES cells and facilitate the generation and culture of these cells. Therefore, the culture of stem cells for ten or more or thirty or more passages is prima facie obvious because the longer the culture the greater the number of stem cells obtainable. Repeating the exposure to activin-A at least one time would naturally from or is implicit in maintaining ES cells in the undifferentiated state for multiple passages. See, for example, Williams, Figure 2. The invention is prima facie obvious over the prior art.

Conclusion

No claims are allowable.

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FEBRUARY 9, 2011